Attachment 1

Transdermal Permeation of Fentanyl from Silicone Pressure Sensitive Adhesive Blends

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ABSTRACT

Amine compatible silicone pressure sensitive adhesives release fentanyl rapidly through human cadaver skin with little control of permeation rate. The addition of standard silicone pressure sensitive adhesive to a simple platform containing 2.5% fentanyl in amine compatible silicone adhesive reduces fentanyl permeation rates and results in the controlled release of fentanyl through human cadaver skin.

INTRODUCTION

Amine compatible silicone pressure sensitive adhesive (PSA) was developed to provide effective adhesion for transdermal delivery devices (TDD) containing base drugs with a pKa >8. Essentially, most of the adhesive's silanol groups (Si-OH) are substituted by methyl groups (Si-CH_3) to yield an adhesive that exhibits sufficient tack for instantaneous skin adhesion[1] Currently, amine compatible silicone PSA is used commercially as an adhesive layer for transdermal delivery of fentanyl. These systems require the use of ethanol containing reservoirs and rate controlling membranes to achieve controlled drug permeation. Here, simplified drug in adhesive (DIA) systems, utilizing amine compatible silicone PSA and standard silicone PSA blends have been evaluated for their ability to control drug permeation rates.

EXPERIMENTAL METHODS

TDDs were prepared from the following materials:

Fentanyl Base – Mallinckrodt Inc.

Silicone BIO-PSA® 7-4202 – Dow Corning Corp.

Silicone BIO-PSA® 7-4502 – Dow Corning Corp.

The following compositions were produced by casting polymer blends on 3M™ Scotchpak™ 1022 release liner, drying for 5 minutes at RT, then 5 minutes at 92° C in a convection oven. Dried matrix was laminated to the polyester side of 3M™ Scotchpak™ 9732 backing and had a coat weight of 10.0 +/- 0.5 mg/cm^2.

	Formula Number				
	1	2	3	4	5
Fentanyl	2.5	2.5	2.5	2.5	2.5
BIO-PSA® 7-4202 (amine comp.)	97.5	72 5	47.5	22.5	0
BIO-PSA® 7-4502 (standard)	0	25.0	50.0	75.0	97.5

Solvated components were measured to achieve (%) dry weight listed above.

A permeation study was performed with stratum corneum obtained from split thickness cryopreserved cadaver skin by the heat separation technique. 0.5cm^2 circular patches (n=3) were cut from adhesive laminate, placed upon stratum corneum and mounted on modified Franz cells that were magnetically stirred at ~300rpm and maintained at 32°C. The receiving solution was 7.5 ml of 0.9% NaCl and 0.01% NaN_3 which was replaced at each sample point. The permeation samples were analyzed by HPLC using a Phenomenex® Columbus C8, 5µm, 10.0 x 0.46cm column with a flow rate of 1.5 ml/min. The detector is set at 210 nm. Mobile phase is: buffer:acetonitrile:methanol (50:30:20). Buffer is 10mM KH_2PO_4 + 4.5 mM OSA at pH 3.0

RESULTS AND DISCUSSION

Drug became crystallized in formula 1, therefore this matrix was not included in the permeation study. Figure 1 illustrates the results obtained for drug permeation from the 4 remaining formulas. Table 1 presents the permeation rates determined for these 4 formulas over the duration of the three day study.

Figure 1

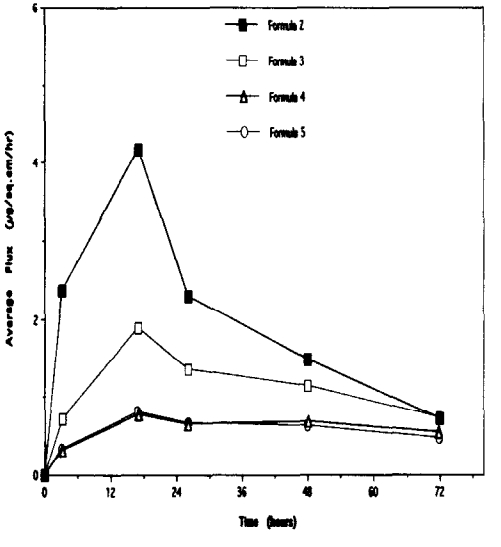

Table 1

Formula Number	Permeation Rate (µg/cm^2/hr)
2	1.92
3	1.20
4	0.65
5	0.62

The addition of standard silicone PSA provided the solubility in the matrix to mediate release of drug through the skin, similar to results found when blending silicone and acrylic PSAs[2]. Previously, according to Kanios et al., blends of silicone PSAs have been used for the manipulation of adhesive performance properties (i.e. peel and shear)[3]. These results indicate that the solubility parameters of silicone adhesives differ substantially enough to permit effective manipulations of drug release rates through human cadaver skin.

CONCLUSION

Simple silicone blend DIA systems have the ability to control fentanyl release rates effectively. Fentanyl permeation is slowed as the silanol content of the matrix increases. Investigation of improving flux rate to reduce patch size while utilizing this controlled release technique could lead to highly efficient systems with very low irritation potential.

References

1 Woodard, J.T. and Metevia, V.L. Transdermal Drug Delivery Devices with Amine-resistant Silicone Adhesives. US Patent 4,655,767 (assigned to Dow Corning Corp.)

2 Miranda, J. and Sablotsky S. Solubility Parameter Based Drug Delivery System and Method for Altering Drug Saturation Concentration. US Patents 5,474,783 and 5,656286 (assigned to Noven Pharmaceuticals, Inc.)

3 Kanios, D.P., Mantelle, J., Nartker, L.S., Raul, V.A., Ulman, K.L. Pressure Sensitive Adhesive Compositions for Transdermal Delivery Devices. US Patent 6,337,086 (assigned to Dow Corning Corp.)

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